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Tremor and Other Hyperkinetic Movements

Articles

Prescriptions for Alpha Agonists and Antipsychotics in Children and Youth with Tic Disorders: A Pharmacoepidemiologic Study

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Abstract

Background: Trends in the use of antipsychotics and alpha agonists for the treatment of tic disorders in Canadian children, and how closely these trends align with evidence-based guidelines on the pharmacotherapy of tic disorders, have not been explored.

Methods: IQVIA's Canadian Disease and Therapeutic Index, a survey-based data set, was used to identify prescription patterns by physicians. Respondents recorded all patient visits during a 48-hour period in each quarter of the year, including patient age, gender, drug recommendation and therapeutic indication. Recommendations for alpha agonists and antipsychotics from 2012 to 2016 were analysed for children and adolescents with tic disorders.

Results: Risperidone and clonidine were the most commonly recommended medications for tic disorders over the study period, with 36,868 and 35,500 recommendations in 2016, respectively. Recommendations for clonidine increased over the study period, whereas those for risperidone decreased. Guanfacine (approved in Canada in 2013) was used less frequently than clonidine. Clonidine was more frequently recommended than antipsychotics in children younger than 6, in whom antipsychotic recommendations were uncommon. Aripiprazole was the second most commonly recommended antipsychotic for tic disorders, with 22,892 recommendations in 2016. Of the first-generation antipsychotics, pimozide was most commonly recommended (11,334 recommendations in 2016); haloperidol was infrequently recommended.

Discussion: The trends observed are in line with guideline recommendations reflected in the decreasing use of risperidone, and the growing use of clonidine and guanfacine. The growing use of aripiprazole is likely due to emerging evidence from clinical trials supporting its efficacy for tics. Recommendations for pimozide and haloperidol were limited, likely due to the greater adverse effects associated with these medications.

Keywords: Tic disorders, Tourette syndrome, pharmacoepidemiology, antipsychotics, alpha agonists

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Ethics Statement: The data used for this study were drawn from IQVIA's Canadian Disease and Therapeutic Index (CDTI). This is a proprietary source of data belonging to IQVIA and therefore not publicly available. IQVIA is a multinational company offering consultative and analytical services pertaining to their data products, focusing chiefly on clinical research and health information technologies. As noted in the Methods section, participating physicians completed an anonymised record of all patient visits during a 48-hour period in each quarter of the year. Informed consent was not required as no personal identifying information was collected. No institutional review board was required, as the research did not entail experimental investigation of human participants.

Introduction

Tic disorders have been conceptualised as hyperkinetic movement disorders, manifesting as brief and intermittent movements (motor tics) or sounds (phonic tics), and further characterised by their highly repetitive nature and waxing-and-waning course.[1] Motor tics are typically sudden and may appear as simple motor tics (e.g., blinking, shoulder-shrugging and facial grimacing), or as complex motor tics resembling gestures or other elements of normal behaviour. Phonic tics include sniffing, clearing of the throat, grunting, chirping or more complex vocalisations such as words or phrases. Frequently, a premonitory sensation or urge heralds the appearance of a tic.[1,2] The most common cause of tics in childhood is Tourette syndrome (TS), which is characterised by both motor and phonic tics and is often accompanied by psychiatric comorbidities including attention deficit hyperactivity disorder (ADHD) or obsessive-compulsive disorder (OCD). The Canadian prevalence estimate of diagnosed TS in youth is 6.03 per 1,000 in males and 0.48 per 1,000 in females.[3]

Medications and behavioural interventions comprise the main treatments for tics.[4–6] However, tic severity and the degree to which patients suffer physical, emotional or social distress are often such that no treatment is necessary.[4,7] Oral medications for tics include alpha 2-adrenergic agonists, antipsychotics, topiramate and tetrabenazine.[4] A behavioural intervention for which there is strong evidence is Comprehensive Behavioural Interventions for Tics (CBIT), which includes habit reversal therapy (HRT) as its primary component.[8] This is considered the first-line treatment for tics in patients over the age of 9 and entails self-monitoring of tics and their premonitory urges, with the goal of learning to perform a counteracting behaviour that is incompatible with the tic.[8] After CBIT/HRT, medications form the second tier of treatment for tics, based on collaborative decision-making with parents.[7] Alpha agonists, such as clonidine and guanfacine, have been identified by Roessner et al. as commonly prescribed among European experts in TS, with clonidine as the second most commonly prescribed medication for tics according to their survey.[9] Canadian guidelines put forward a strong recommendation for alpha agonists, as a result of moderately strong evidence of efficacy coupled with their favourable side effect profile relative to antipsychotic medications.[8] Antipsychotic medications are well studied and have been widely used in the treatment of tics and include both first-generation agents, such as pimozide and haloperidol, and second-generation agents, such as risperidone and aripiprazole.[4] The efficacy of pimozide and haloperidol in the treatment of tics is well established, as is their association with metabolic side effects, drug-induced movement disorders and QTc prolongation.[9,10] Similar evidence exists supporting the efficacy of risperidone and aripiprazole, as well as concerns regarding side effects.[8–10] Although high-quality evidence supports the efficacy of several antipsychotics, Canadian guideline recommendations for these are weak owing to unfavourable side effect profile.[4,8] Although these data are generally elusive, it is vital to study trends in prescribing for paediatric tic disorders and to investigate whether or not such trends fall in line with evidence-based guidelines.

As noted above, in the North American context, Pringsheim et al. evaluated the evidence pertaining to several therapies for tics and made strong recommendations for clonidine and guanfacine for the treatment of tics in children, but weak recommendations for many antipsychotics due to high rates of side effects (including metabolic effects such as weight gain), despite the strong evidence supporting their efficacy.[8] An important distinction thus emerges between evidence of efficacy and strength of recommendation for a given treatment. Pringsheim et al. used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, in which there is a separation between quality of evidence and strength of recommendations.[11] Based on risk of bias, the quality of evidence in the GRADE system may be rated as high, moderate, low or very low. Two grades of recommendation – strong and weak – give an indication of when the benefits of a treatment clearly outweigh the risk of side effects. Acknowledgment of values, preferences and circumstances that may affect recommendations is part of the GRADE system and figures largely in the case of weakly recommended treatments. That is to say, a treatment may merit a strong recommendation when it can be recommended to most patients in most circumstances. In the case of a weakly recommended treatment, the balance of risks and benefits is less favourable, and therefore the best course of action depends strongly on patient values, preferences and circumstances. A simultaneous appreciation of quality of evidence and strength of recommendation thus allows for a medication supported by high-quality evidence to nevertheless receive a weak recommendation.

Elucidating trends in prescribing may be approached through surveys of patients and physicians.[5,9,10] On a larger scale, database approaches may shed light on prescribing trends in Canada. This is an established approach, the utility of which was demonstrated using the Canadian Disease and Therapeutic Index (CDTI) in the study of antipsychotic use in Canada.[12] Similarly, private vendors of physician prescribing data have been leveraged for pharmacoepidemiologic study, as one group showed in their research on the increasing use of selective serotonin reuptake inhibitors in children.[13] In the present study, data were drawn from the CDTI and used to infer prescribing trends for children with tic disorders, attending to drug class, molecule and patient age. These were compared with current guidelines for the treatment of tic disorders in children. The aim was to gauge how closely the trends approximate existing guidelines.

Methods

IQVIA's CDTI was used as a proxy measure of prescriptions for children with tic disorders. CDTI is a survey-based data set that collects treatment data from a sample of office-based physicians in Canada and allows for analyses to identify pharmacoepidemiologic patterns by drug, indication, patient demographics and physician specialty. A random sample of physicians, stratified by region in Canada and by office-based specialty, is requested to complete a survey of patients they have seen during the reporting period, and capturing information on patient demographics, diagnosis and prescribing decisions, among other information. All major office-based specialties are represented, with representation based on proportionality. Some specialties with very few physicians are over-sampled to allow for greater reliability in these areas. A minimum of 85% of reporting physicians in a current period are

maintained from the previous reporting period. Statistical weighting, stratified by region and specialty, of the reported prescribing from the sample physicians to the universe of physicians is conducted to derive national projections. Projection factors are adjusted to compensate for the over-sampling. CDTI is an ideal source for this type of study as compared to administrative prescription records, as the latter are typically collected in specific Canadian populations (e.g., those covered by publicly or privately funded drug plans) and prescribed certain drugs (covered by those plans), often without information about indication or prescribing intent.

Participating physicians complete an anonymised record of all patient visits during a 48-hour period in each quarter of the year, including patient age, gender, drug recommendation (prescribed drug) and reason for recommendation (therapeutic indication). Rate of prescription purchases was not recorded in this database. Informed consent was not required as no personal identifying information was collected.

The data analysed for this study reflected the time period from 2012 to 2016, or from 2010 to 2016 in the specific case of antipsychotic medications, and were reviewed as a spreadsheet in Microsoft Excel (2017; Redmond, WA, USA). Drug recommendation totals were taken for all column entries designated as "Tic Disorder". The medication class and molecules analysed for all tic disorder entries included the alpha agonists clonidine and guanfacine; the antipsychotics class represented as first-generation antipsychotics (chlorpromazine, chlorprothixene, droperidol, flupentixol, fluphenazine, fluspirilene, haloperidol, loxapine, mesoridazine, methotrimeprazine, periciazine, perphenazine, pimozide, piperacetazine, pipotiazine, prochlorperazine, promazine, thioprapazate, thioproperazine, thioridazine, trifluoperazine and zuclopenthixol); and the antipsychotics class represented as second-generation antipsychotics (aripiprazole, asenapine, clozapine, lurasidone, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone). The CDTI allowed for the drug recommendation totals to be further subdivided by patient age into three groups: those aged 1–6 years, 7–12 years and 13–18 years. Similar age categories have been used in previous studies.[14–16] Bachmann et al. have shown that psychopharmacological treatment of tics is highest in teenaged patients.[17] Overall, the focus of the present study was on drug recommendations for the specific indication of tic disorders, in patients belonging to the three age categories listed above.

The data pertaining to physician specialty list their medication recommendations by medication class/molecule but not by indication. Therefore, the analyses in the current study, which are specific to recommendations for the treatment of tic disorders, capture recommendations made by general practitioners, neurologists, psychiatrists and paediatricians. Furthermore, the indication "Tic Disorder", as listed in the CDTI, is not subdivided further into the specific diagnosis of TS.

Results

The overall trends revealed by the CDTI were for greater recommendations for antipsychotics than for alpha agonists, with a relatively small decrease in recommendation totals over time for antipsychotics, and a steady increase in the number of recommendations for alpha agonists. In the case of antipsychotic medications, recommendation totals were 85,010 in 2010 and fell to 71,094 in 2016. The alpha agonists clonidine and guanfacine were collectively recommended in increasing amounts, from 17,850 in 2012 (reflecting clonidine alone) to 45,752 in 2016 (reflecting both clonidine and guanfacine).

Medications in the alpha agonist class

Table 1 summarises the recommendations for medications in this class by year and age category. Combining all three age categories, recommendations for clonidine were higher than guanfacine. Clonidine was recommended in increasing amounts to patients in all three age categories. Recommendations for clonidine were consistent and grew steadily, with totals of 17,850 in 2012 rising to 35,550 in 2016. The trend for growing recommendations for clonidine was present across the three age groups from 2012 to 2016, with a greater-than-threefold increase in those aged 1–6, a nearly one-and-a-half-fold increase in those aged 7–12 and nearly doubling in those aged 13–18 years.

The trend of increasing recommendations for guanfacine was noted in two age categories only – in those aged 7–12 and 13–18 years – whereas patients aged 1–6 years contributed no data in terms of guanfacine recommendations. In patients aged 7–12, guanfacine

Table 1. **Alpha Agonist Medications by Drug, Year and Patient Age**

Medication	2012	2013	2014	2015	2016
Clonidine 1–6 years	–	2,430	6,820	4,045	8,416
Clonidine 7–12 years	12,320	13,420	6,160	4,182	16,831
Clonidine 13–18 years	5,530	5,870	5,100	16,385	10,303
Clonidine TOTAL	17,850	21,720	18,080	24,612	35,550
Guanfacine 1–6 years	–	–	–	–	–
Guanfacine 7–12 years	_	_	2,530	_	10,202
Guanfacine 13–18 years	_	_	5,490	28,004	_
Guanfacine TOTAL			8,020	28,004	10,202

recommendation totals increased roughly fourfold when comparing 2016 to 2014. Similarly, amongst patients aged 13–18, guanfacine recommendation totals increased by roughly a factor of 5 from 2014 to 2015.

Medications in the antipsychotic class

Table 2 summarises the recommendations for medications in this class by year and age category. Medications in the antipsychotic class, including first-generation (haloperidol and pimozide) and second-generation (aripiprazole, olanzapine, quetiapine and risperidone) agents, have collectively been recommended for tic disorders in children in generally larger numbers than medications in the alpha agonist class. The total number of recommendations for children with tic disorders for all these agents combined was 85,010 in 2010 and showed a net decrease to 71,094 in 2016. Second-generation antipsychotics were generally more prescribed than first-generation antipsychotics. Risperidone remained the most highly recommended antipsychotic medication, followed by aripiprazole, pimozide and quetiapine. Haloperidol and olanzapine were recommended infrequently. The overall trend for antipsychotic recommendations likely reflects an initially higher number of recommendations for risperidone, which then decreased over time but were partially offset by markedly increasing aripiprazole recommendations and a modest increase in quetiapine recommendations.

Discussion

In this study, the CDTI was used to investigate trends in prescribing for tic disorders in children, from 2010 to 2016, with the aim of further studying how closely the trends approximate evidence-based guidelines for treatment of tic disorders in children. Overall, the data show an increase in recommendations for alpha 2-adrenergic agonist medications, an increase in recommendations for aripiprazole and a decrease in those for risperidone. These trends roughly fall within evidence-based guidelines for the treatment of tic disorders in children. Moreover, they are similar to prescribing trends in parts of Europe.

Table 2. **Antipsychotic Medications by Drug, Year and Patient Age**

Medication	2010	2011	2012	2013	2014	2015	2016
Pimozide 1–6 years	–	–	–	–	–	–	5,811
Pimozide 7–12 years	12,440	6,250	2,914	3,833	–	3,313	5,523
Pimozide 13–18 years	_	3,220	6,172	7,052	11,372	6,730	–
Pimozide TOTAL	12,440	9,470	9,086	10,885	11,372	10,043	11,334
Haloperidol 1–6 years	-	-	-	-	-	-	-
Haloperidol 7–12 years	–	–	–	–	–	5,848	–
Haloperidol 13–18 years	-	-	-	-	-	-	-
Haloperidol TOTAL	-	-	-	-	-	5,848	-
Aripiprazole 1–6 years	-	-	-	-	-	-	-
Aripiprazole 7–12 years	–	–	3,059	7,666	6,534	10,166	–
Aripiprazole 13–18 years	-	3,140	18,172	7,501	7,578	3,370	22,892
Aripiprazole TOTAL		3,140	21,231	15,167	14,112	13,536	22,892
Risperidone 1–6 years	-	-	-	-	-	-	3,313
Risperidone 7–12 years	27,870	27,360	17,627	13,470	7,665	15,845	26,382
Risperidone 13–18 years	35,670	31,770	5,827	_	10,144	9,218	10,486
Risperidone TOTAL	63,540	59,130	23,454	13,470	17,809	25,063	36,868
Quetiapine 1–6 years	-	-	-	-	-	-	-
Quetiapine 7–12 years	3,090	–	–	–	–	–	–
Quetiapine 13–18 years	2,970	3,260	6,118	–	7,741	–	–
Quetiapine TOTAL	6,060	3,260	6,118	–	7,741	-	-
Olanzapine 1–6 years	-	-	-	-	-	-	-
Olanzapine 7–12 years	2,970	–	–	–	–	–	–
Olanzapine 13–18 years	-	-	-	-	-	-	-
Olanzapine TOTAL	2,970	-	-	-	-	-	-

Note: The hyphen and endash are used to signify that there were no recorded recommendations for that drug in that year for that age group.

Using different approaches, a number of studies have provided insights regarding the effectiveness of various medications for tics, recommendations for their use and prescription trends. Farag et al. retrospectively studied serial drug usage to gain insights into drug effectiveness, thus providing some evidence on the prescribing trends in the authors' local context in London, UK.[10] Prescribing trends were elucidated by studying the common clinical practice of several physicians: serial pharmacotherapy (trying reasonable options until finding an effective medication for treatment of tics). Across a 10-year study period, prescribing behaviours were investigated in terms of the outcome of serial pharmacotherapy. These outcomes were categorised as follows: successful follow-up on last drug used for ≥5 months (a proxy measure for drug success), discharge from clinic on the last drug tried, last drug discontinued with no further switch to a different drug or insufficient follow-up. Farag et al. found that the most commonly prescribed medications for tics were aripiprazole (64%), clonidine (40%), risperidone (30%) and sulpiride (29%).[10]

Roessner et al. provided evidence-based recommendations for the treatment of tics, arguing that the best evidence arising from randomised controlled trials (RCTs) is for the typical antipsychotics haloperidol and pimozide, with some indications that pimozide may be more effective and may have a more favourable adverse reaction profile than haloperidol aside from its potential cardiac effects.[9] For atypical antipsychotics, Roessner et al. argued that the best evidence was available for risperidone.[9] The authors further noted that in German-speaking nations, benzamides (e.g., tiapride and sulpiride) are commonly used as first-line agents.[9] The benzamides are not available for use in Canada.

Roessner et al. collected questionnaire data from members of the European Society for the Study of Tourette Syndrome (ESSTS) regarding their choices for first-, second- and third-choice, and subsequent choices in the treatment of tics, rating each first-choice agent with four points, a second-choice agent with three points, a third-choice agent with two points and additional agents with one point.[9] Most support from experts in the ESSTS was provided for risperidone, with considerable support for clonidine, aripiprazole and pimozide as well.[9] Based on the available evidence, experience with the drug and experts' preference, risperidone was recommended as the first choice by Roessner et al.[9] These results are also consistent with those yielded by Rickards et al., in which 44 members of the ESSTS actively prescribing for paediatric and/or adult TS responded to a survey, showing that risperidone was most commonly prescribed for the treatment of tics.[18]

Hollis et al. combined a systematic review with meta-analyses of pharmacological, behavioural and physical treatments for children and youth with TS.[5] An online national survey of patients and families in the UK found that the most commonly used medications were risperidone, clonidine and aripiprazole.[5] Hollis et al. reported that, at the time of their study, antipsychotics and alpha 2-adrenergic agonists were the only classes with clear RCT-based evidence supporting their short-term effectiveness in the treatment of tics.[5] The authors also argued that aripiprazole may be equally effective when compared to other antipsychotics.[5] Hollis et al. noted relatively weak RCT evidence for topiramate, metoclopramide and desipramine, with recommendations for their use further mitigated by their side effects.[5]

As the CDTI data pertain to Canada, it is prudent to consider Canadian guidelines offered by Pringsheim et al.[8] These may have contributed to the trends revealed by the CDTI, as the authors made strong recommendations for guanfacine and clonidine, both of which were recommended in increasing amounts in the CDTI. The growing number of recommendations for clonidine may be interpreted as an encouraging sign that prescribing trends fall in line with the agents for which there is a lower risk of harm.

However, some concern may be raised regarding risperidone, as the number of recommendations for this medication was more variable. Data from the CDTI show decreasing recommendations for older patients aged 13–18 years, but not the same lasting decrease in younger patients aged 7–12. Additionally, the CDTI data show an increase in aripiprazole. Returning to Canadian guidelines, Pringsheim et al. advised cautious use of antipsychotics, in light of the rate and type of side effects.[8] While the efficacy of haloperidol, pimozide and risperidone is supported by high-quality evidence, they were weakly recommended by Pringsheim et al., given their potential for extrapyramidal, metabolic and hormonal side effects, which arguably limit their use to patients in whom symptom severity may justify these risks.[8] Correspondingly, the CDTI data suggest a degree of caution taken by prescribers, given the decreasing number of recommendations for risperidone. Moreover, the relatively modest recommendations for other antipsychotics suggest discretion in the use of these agents. However, the increase in recommendations for aripiprazole is notable in this regard, given the low quality of evidence supporting its efficacy and the weak recommendation for treating tics at the time the Canadian guidelines were published in 2012.[8] It is notable that the weak recommendation was based on adverse effects and was thus independent of evidence of efficacy. Since that time, two RCTs of aripiprazole versus placebo in children and adolescents with TS have been performed. Both of these trials demonstrated a significant and clinically meaningful improvement in tics with aripiprazole compared to placebo, although metabolic and extrapyramidal side effects were reported. Aripiprazole was approved by the US Food and Drug Administration for the treatment of tics in TS in 2016.[19,20] The increase in the use of aripiprazole from 2012 to 2016 is therefore likely due to the publication of these two positive clinical trials, the first of which was published in 2013, and positive clinical experience with the medication.

While the CDTI data may suggest adherence to Canadian guidelines, the influence of guidelines originating elsewhere merits consideration.

As the current study aimed to elucidate trends in drug recommendations, the concept of adherence to guidelines deserves special attention, as more than just evidence factors into clinical decision-making. In addition to clinical evidence and physician knowledge, it has been shown that patient characteristics and values, as well as those of the patient's parents, affect clinical decision-making.[21] These additional factors may therefore affect the Canadian trends for drug recommendations for children with tic disorders. Medication side effects in particular may also

influence recommendation trends, the efficacy of the medications notwithstanding. In a prospective longitudinal study of antipsychotic use in children, Pringsheim et al. found that metabolic side effects were common, with 26% showing undesirable increases in the body mass index (BMI) percentile, shifting from a healthy weight to the overweight or obese categories.[22] The authors also demonstrated a high rate of extrapyramidal side effects in children taking newer antipsychotics, with 35% having detectable abnormalities, contrary to widely held beliefs regarding expected low rates of such side effects in those taking newer antipsychotics.[22]

The tolerability and side effect profile of alpha agonists warrant close attention, given the impact side effects arguably have on medication use and medication recommendation. In their RCT studying the treatment of ADHD with comorbid TS, the Tourette's Syndrome Study Group reported sedation as a common side effect of clonidine, with 28% reporting moderate to severe sedation.[23] Joo and Kim studied the tolerability of an extended release formulation of clonidine as a treatment of ADHD and/or TS, finding sedation to be the most common adverse effect, reported in 31% of patients.[24] This was followed by dizziness (17.2%), and then fatigue, insomnia, night terrors, hypotension, nausea, chest discomfort, headache and aggravation of tics, all of which affected less than 4% of patients.[24] In a study by Cavanna et al. of the tolerability of clonidine in adults with TS, 47.2% reported side effects, although in most cases these were mild and occurred with higher starting doses, with sedation and headache being the most commonly reported.[25] These findings are by and large consistent with the strong recommendation for alpha agonists received in Canadian guidelines, when compared to the side effect profile of first- and second-generation antipsychotic medications.

Certain limitations may have affected the current study. For the treatment of tic disorders in children, it must be noted that strong evidence exists for CBIT, which includes HRT.[5,8,26,27] It is unclear how many patients in the CDTI were receiving CBIT, and so it is unclear how trends revealed in the CDTI may reflect adherence to guidelines, without data pertaining to the adoption and recommendation of CBIT and HRT. The CDTI data reflect reporting from a 48-hour period during each quarter, which may or may not be representative of trends year-round. The projected recommendation totals also introduce variability, both within and between physicians, perhaps failing to accurately capture the number of medication recommendations for tic disorders between the reporting periods. The total number of medication recommendations does not show what proportion of patients with tic disorders are offered specific medications. It is also unknown if drug selection was influenced by the presence of particular comorbidities, or by tic severity or prior drug responsiveness. Whether or not drug recommendations varied by physician training, specialisation or experience is also unknown based on the CDTI data. Assuming the diagnosis of tic disorder was rendered accurately, there are several aetiologies for tics, and this is not captured by the CDTI data. However, this may have little impact, as the approach to pharmacotherapy is based on tic severity and not aetiology. Taken together, the above may cast some doubt on the validity of medication recommendations as a measure of adherence to guidelines. Similarly, as tic disorders are uncommon, and not all cases are treated with pharmacotherapy, there is uncertainty regarding how accurately the projected drug recommendation totals reflect the actual treatment of patients, and thus how closely these align with evidence-based guidelines. Finally, medication recommendations are not a direct measure of dispensed medications, and therefore trends in recommendations may not precisely reflect trends in the use of medications.

Despite the caveats inherent to this study, the use of databases to infer trends is becoming increasingly well established.[13,28,29] There is arguably a reciprocal relationship between the use of databases to infer adherence to guidelines and to improve data collection to develop or update guidelines. Oyinlola et al. investigated whether "real world evidence", as reflected in large databases, influenced medical practice in the UK in 12 disease areas.[30] The authors found an increasing trend in the use of "big data" extracted from databases to update clinical practice.[30] A reasonable counterargument against the usefulness of databases is that an understanding of how drug recommendations evolve may be better achieved by following prescriptions written by the same physicians. A longitudinal review of records and prescription histories could therefore clarify whether recommendations represent new prescriptions or prescription renewals, confirm the accuracy of diagnoses, establish tic severity and comorbidities, and reveal the sequence of drug recommendations and the rationale underlying recommendations, such as newly published evidence. While these points may weaken the validity of databases for evaluating trends, in the case of the CDTI, the sample of 652 physicians for this study remained fairly constant over the reporting period, with more than 85% of the sample retained from one year to the next. Furthermore, an advantage of using the CDTI is that it provides population-based data on prescribing trends, rather than those within a single practice.

In summary, medication recommendation trends in Canada for children with tic disorders are consistent with evidence-based guidelines, with reasonable projections for increases in the use of alpha 2-adrenergic agonists. Future studies may focus on how databases such as the CDTI may be applied as a tool not only for ongoing monitoring but also for physician education to help improve understanding of healthcare delivery and inform physician education.[13,28–32]

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